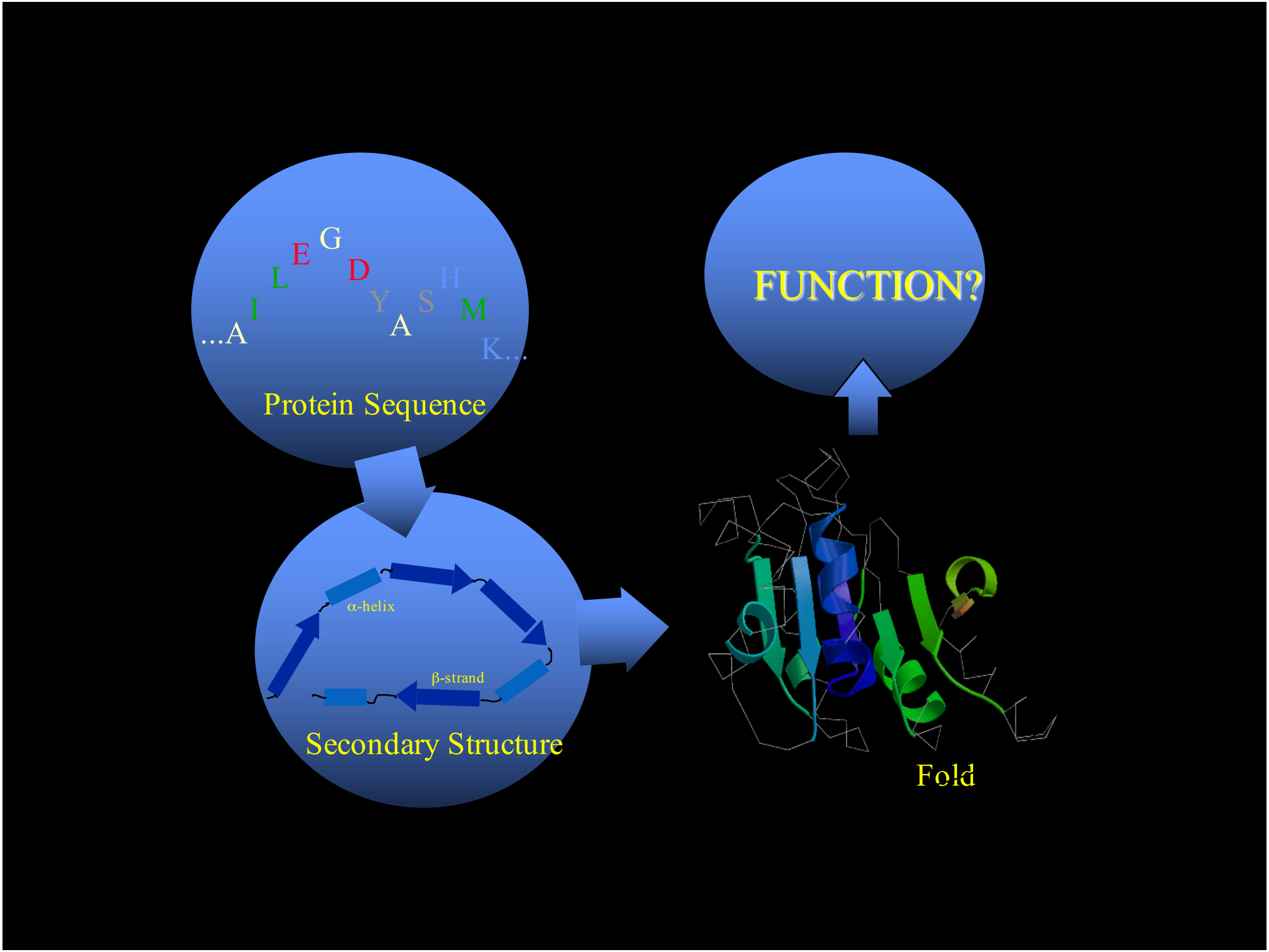
JPred and Jnet: Protein Secondary Structure Prediction

www.compbio.dundee.ac.uk/jpred


...A
I
L
E
G
D
H
Y
A
S
M
K...
Protein Sequence
α-helix
β-strand
Secondary Structure
FUNCTION?
Fold

What is the difference between JPred and Jnet???

- JNet refers to the prediction “engine” that does the work. The current version of this is Version 2.3.1

- JPred refers to the website. This uses JNet and other tools to do predictions and present them in different ways.

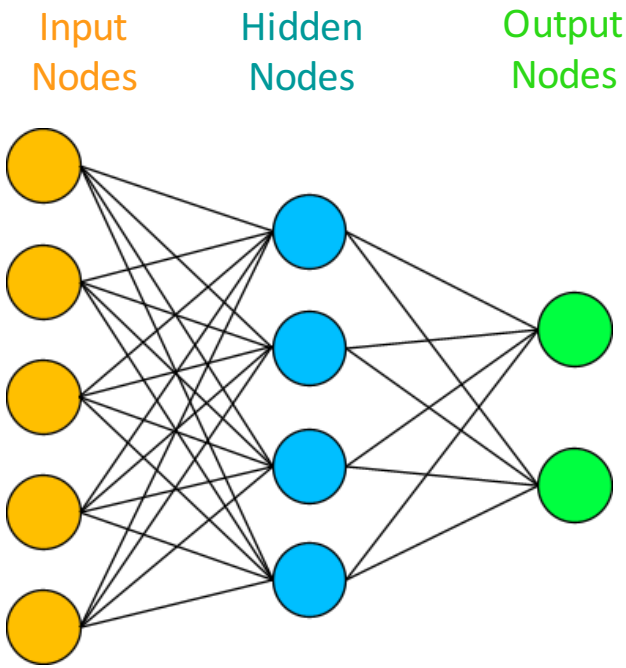
History of JPred/JNet

- 1987: Zpred: First predictor that used multiple sequence alignment
- 1999: Jpred 1: Did prediction by combining prediction methods developed by different groups that worked from multiple sequence alignments
- 2000: JNet 1: Multiple neural network predictor replaced all other methods in JPred
- 2002: JPred 2: Retraining JNet – improved accuracy
- 2009: JPred 3: Retraining JNet, algorithm improvements to Jnet and website refresh
- 2015: Jpred 4: Retraining JNet, major website improvements

Neural Network???

Machine learning method

Neural Networks



- Inductive method of learning
- Supervised learning
  - Inputs and outputs provided
- Dependent on 'quality' of observations
  - Representative
  - Unbiased (non-redundant)

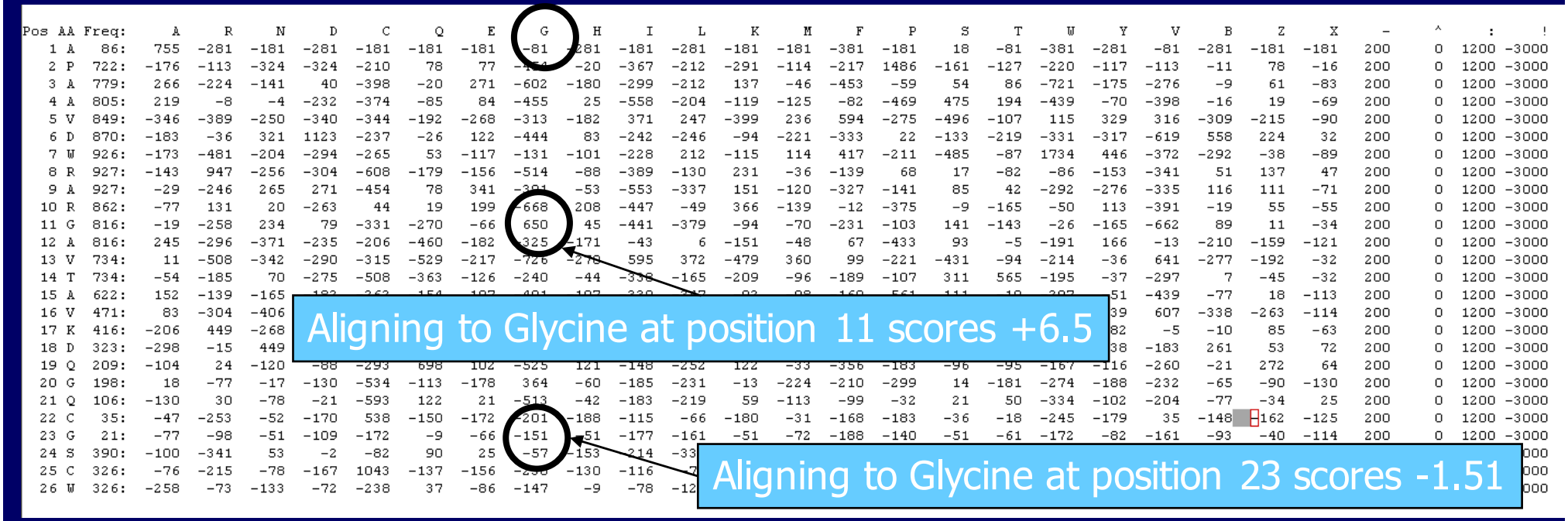
Training and Testing JPred4/Jnet 2.3.1

- You need training data – where you know the answer.
  - We use a set of PDB domains of known structure from the SCOP domains database
- Testing
  - 1. Cross-validation on 1208 domains
  - 2. Blind test on 150 domains not used in training

Neural Network Inputs

- Generate alignments for each sequence by searching UniRef90 with PSI-BLAST
- Make profiles:
  - Position-Specific Scoring Matrix (PSSM)
  - Hidden Markov Model (HMMer3)
- Earlier versions of JNet/Jpred had more inputs.

Profiles give position-specific scoring



Pos	AA	Freq:	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V	B	Z	X	-	^	:	!
1	A	86:	755	-281	-181	-281	-181	-181	-181	-81	-281	-181	-281	-181	-181	-381	-181	18	-81	-381	-281	-81	-281	-181	-181	200	0	1200	-3000
2	P	722:	-176	-113	-324	-324	-210	78	77	-4[illegible]	-20	-367	-212	-291	-114	-217	1486	-161	-127	-220	-117	-113	-11	78	-16	200	0	1200	-3000
3	A	779:	266	-224	-141	40	-398	-20	271	-602	-180	-299	-212	137	-46	-453	-59	54	86	-721	-175	-276	-9	61	-83	200	0	1200	-3000
4	A	805:	219	-8	-4	-232	-374	-85	84	-455	25	-558	-204	-119	-125	-82	-469	475	194	-439	-70	-398	-16	19	-69	200	0	1200	-3000
5	V	849:	-346	-389	-250	-340	-344	-192	-268	-313	-182	371	247	-399	236	594	-275	-496	-107	115	329	316	-309	-215	-90	200	0	1200	-3000
6	D	870:	-183	-36	321	1123	-237	-26	122	-444	83	-242	-246	-94	-221	-333	22	-133	-219	-331	-317	-619	558	224	32	200	0	1200	-3000
7	W	926:	-173	-481	-204	-294	-265	53	-117	-131	-101	-228	212	-115	114	417	-211	-485	-87	1734	446	-372	-292	-38	-89	200	0	1200	-3000
8	R	927:	-143	947	-256	-304	-608	-179	-156	-514	-88	-389	-130	231	-36	-139	68	17	-82	-86	-153	-341	51	137	47	200	0	1200	-3000
9	A	927:	-29	-246	265	271	-454	78	341	-3[illegible]	-53	-553	-337	151	-120	-327	-141	85	42	-292	-276	-335	116	111	-71	200	0	1200	-3000
10	R	862:	-77	131	20	-263	44	19	199	-668	208	-447	-49	366	-139	-12	-375	-9	-165	-50	113	-391	-19	55	-55	200	0	1200	-3000
11	G	816:	-19	-258	234	79	-331	-270	-66	650	45	-441	-379	-94	-70	-231	-103	141	-143	-26	-165	-662	89	11	-34	200	0	1200	-3000
12	A	816:	245	-296	-371	-235	-206	-460	-182	325	-171	-43	6	-151	-48	67	-433	93	-5	-191	166	-13	-210	-159	-121	200	0	1200	-3000
13	V	734:	11	-508	-342	-290	-315	-529	-217	-726	-278	595	372	-479	360	99	-221	-431	-94	-214	-36	641	-277	-192	-32	200	0	1200	-3000
14	T	734:	-54	-185	70	-275	-508	-363	-126	-240	-44	-338	-165	-209	-96	-189	-107	311	565	-195	-37	-297	7	-45	-32	200	0	1200	-3000
15	A	622:	152	-139	-165	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	51	-439	-77	18	-113	200	0	1200	-3000
16	V	471:	83	-304	-406	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	39	607	-338	-263	-114	200	0	1200	-3000
17	K	416:	-206	449	-268	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	82	-5	-10	85	-63	200	0	1200	-3000
18	D	323:	-298	-15	449	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	38	-183	261	53	72	200	0	1200	-3000
19	Q	209:	-104	24	-120	-88	-293	698	102	-525	121	-148	-252	122	-33	-356	-183	-96	-95	-167	-116	-260	-21	272	64	200	0	1200	-3000
20	G	198:	18	-77	-17	-130	-534	-113	-178	364	-60	-185	-231	-13	-224	-210	-299	14	-181	-274	-188	-232	-65	-90	-130	200	0	1200	-3000
21	Q	106:	-130	30	-78	-21	-593	122	21	-513	-42	-183	-219	59	-113	-99	-32	21	50	-334	-102	-204	-77	-34	25	200	0	1200	-3000
22	C	35:	-47	-253	-52	-170	538	-150	-172	-201	-188	-115	-66	-180	-31	-168	-183	-36	-18	-245	-179	35	-148	-162	-125	200	0	1200	-3000
23	G	21:	-77	-98	-51	-109	-172	-9	-66	-151	-51	-177	-161	-51	-72	-188	-140	-51	-61	-172	-82	-161	-93	-40	-114	200	0	1200	-3000
24	S	390:	-100	-341	53	-2	-82	90	25	-57	-153	214	-33	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	000
25	C	326:	-76	-215	-78	-167	1043	-137	-156	-2[illegible]	-130	-116	-7[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	000
26	W	326:	-258	-73	-133	-72	-238	37	-86	-147	-9	-78	-12[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	000

Aligning to Glycine at position 11 scores +6.5

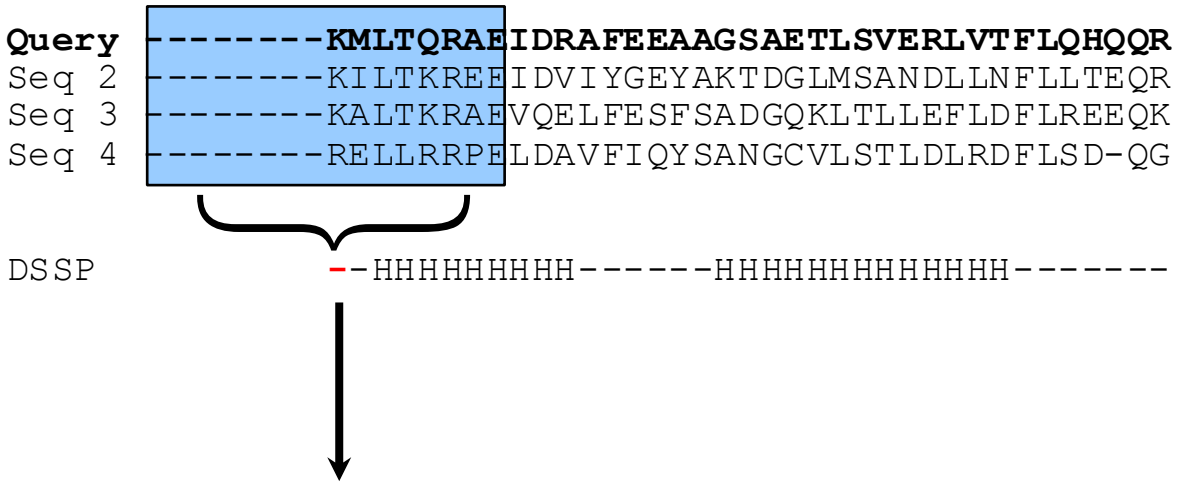
Aligning to Glycine at position 23 scores -1.51

This emphasises position-specific features of the protein family

Compared to Gly-Gly score of 0.6 in the BLOSUM62 matrix.

Neural Network Outputs

- DSSP definitions of secondary structure reduced from 8- to 3-state
  - H: Helix
  - E or B: Extended strand
  - Everything else: coil

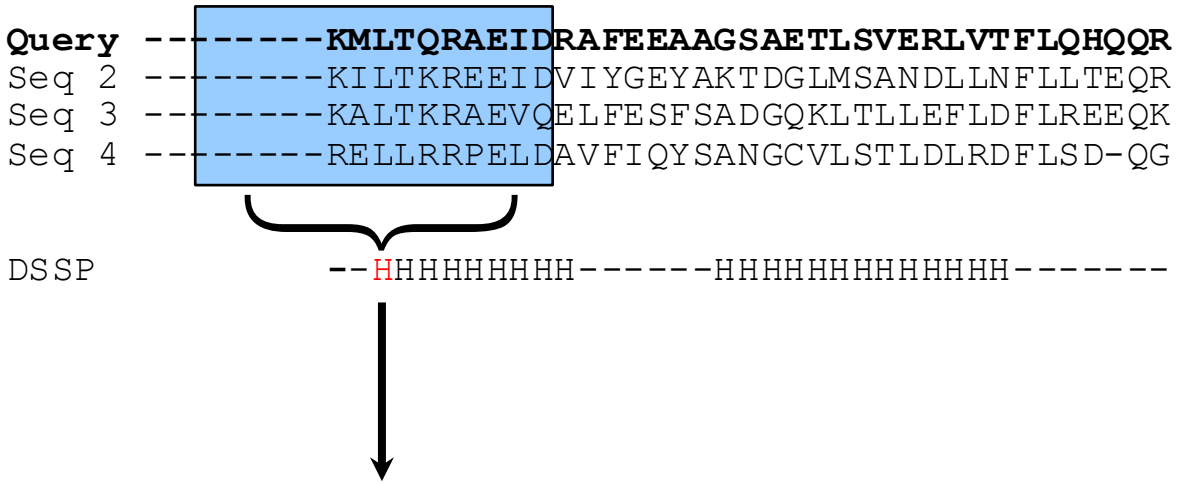


Each position in the input vector is the score for an amino acid within the window

```
# Input 1
0 0 0 0 0 0 0 0 0.9820 0.1192 0.28689 ...
# Output 1
1 0 0
```

Each position in the input vector is the score for an amino acid within the window

```
# Input 2
0 0 0 0 0 0 0 0.9820 0.1192 0.28689 0.0474 ...
# Output 2
1 0 0
```



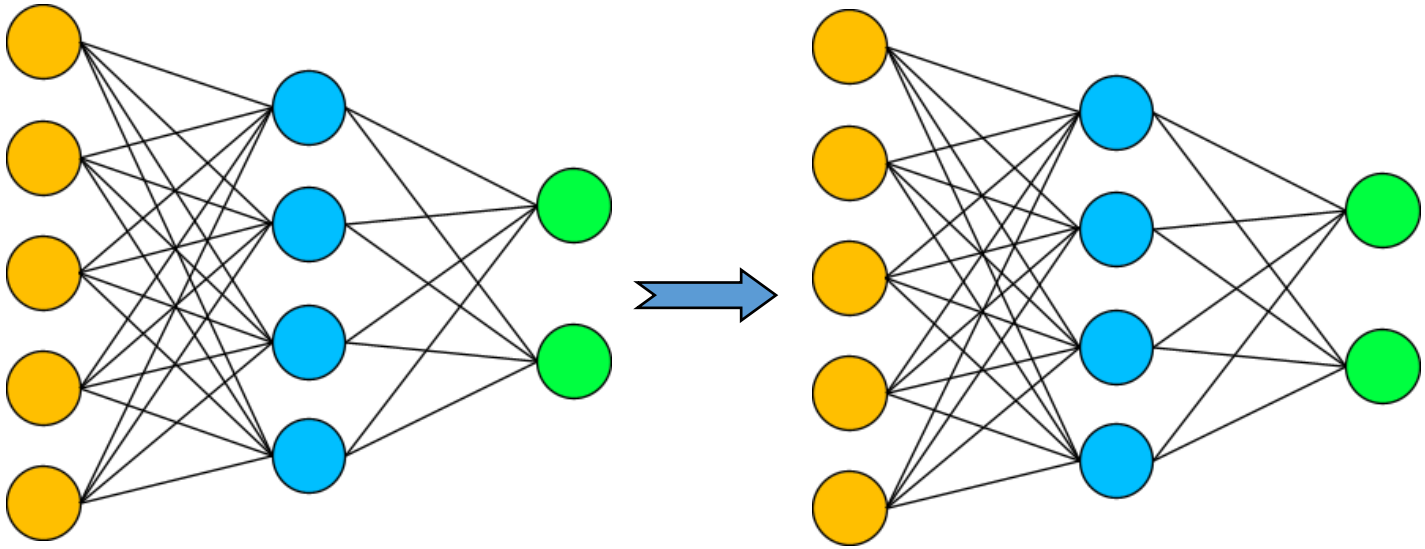
Each position in the input vector is the score for an amino acid within the window

```
# Input 3
0 0 0 0 0 0 0.9820 0.1192 0.28689 0.0474 0.1192 ...
# Output 3
0 0 1
```

Two-Layer Ensemble

Sequence to Structure

Structure to Structure



E-EEEEH-------HHH-HHH-HHH-HE-

--EEEEE-------HHHHHHHHHHHHHH-

Actually, both have hundreds of inputs and three outputs – only two outputs shown for simplicity

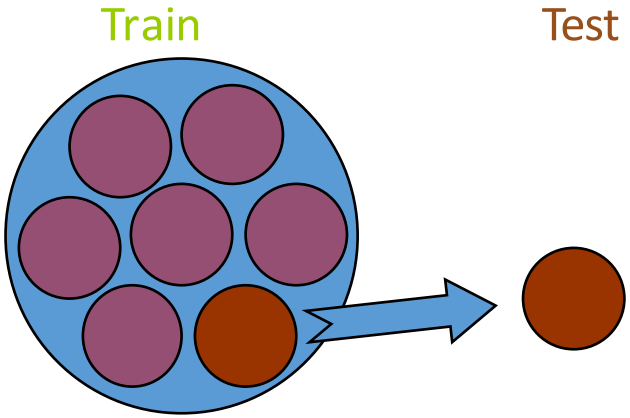
Training and Testing JPred4/Jnet 2.3.1

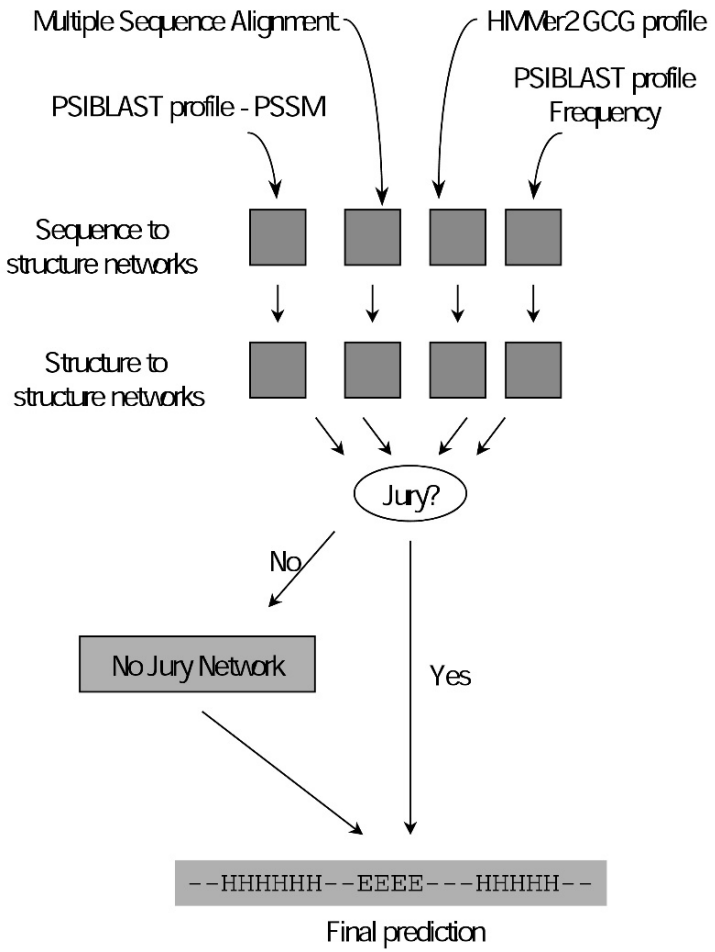
- You need training data – where you know the answer.
  - We use a set of PDB domains of known structure from the SCOP domains database

- Testing
  - 1. Cross-validation on 1358 domains
  - 2. Blind test on 150 domains not used in training

Cross-validation training

- *'Blind'* data - removed subset
- *k*-fold Cross-Validation (887 seqs)
  - Divide training data into *k* groups, train on *k*-1 and test on remainder. Do this *k* times.

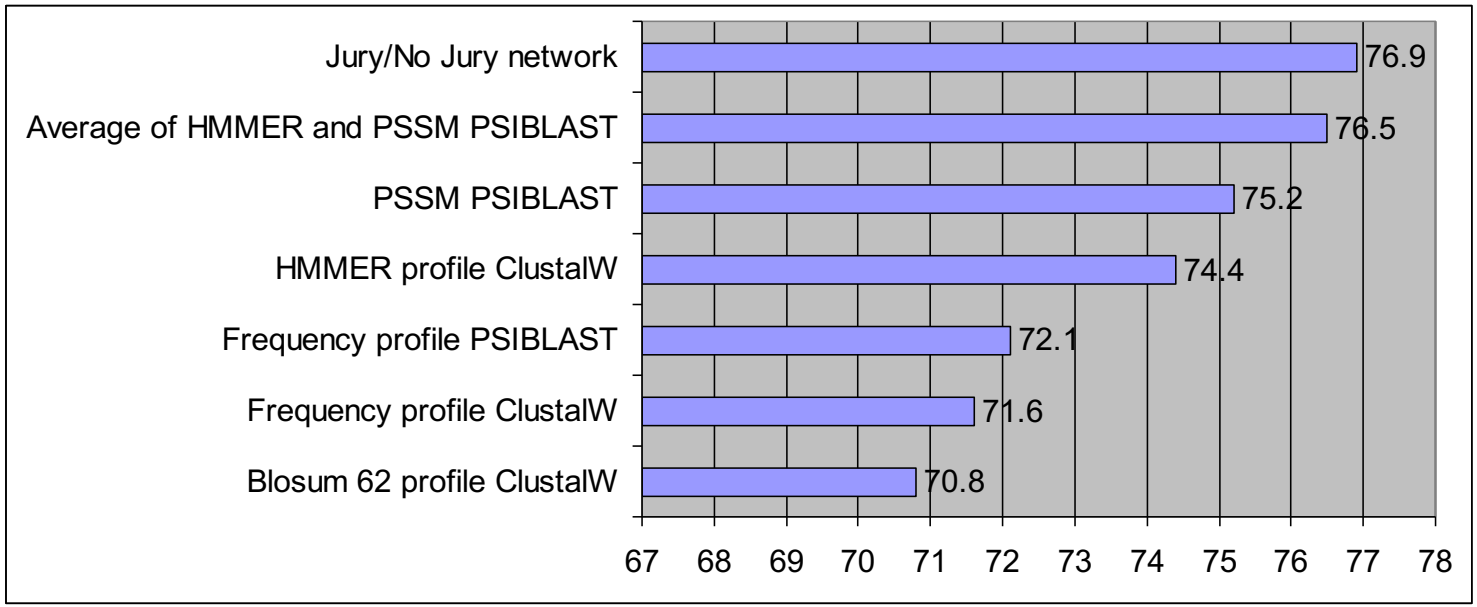




Jnet Version 1: Multiple methods of presenting alignment information.

If alternative networks do not agree, predict with network trained on difficult to predict regions.

JNet Version 1: Effect of Different Alignment Inputs



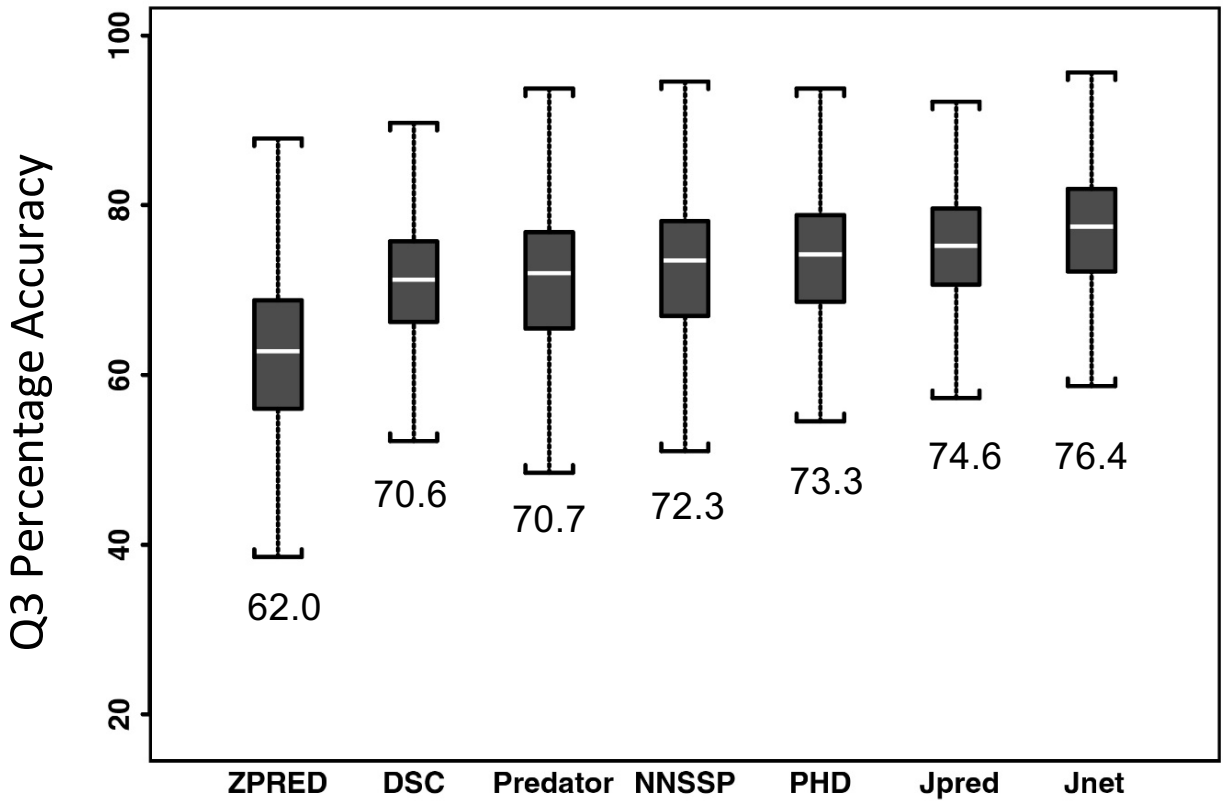
Average Percentage Accuracy
(7-fold cross-validation on 480 proteins)

JNet also accurately predicts whether amino acids will be buried or exposed in the folded structure of the protein.

Blind Test

JNet Version 1

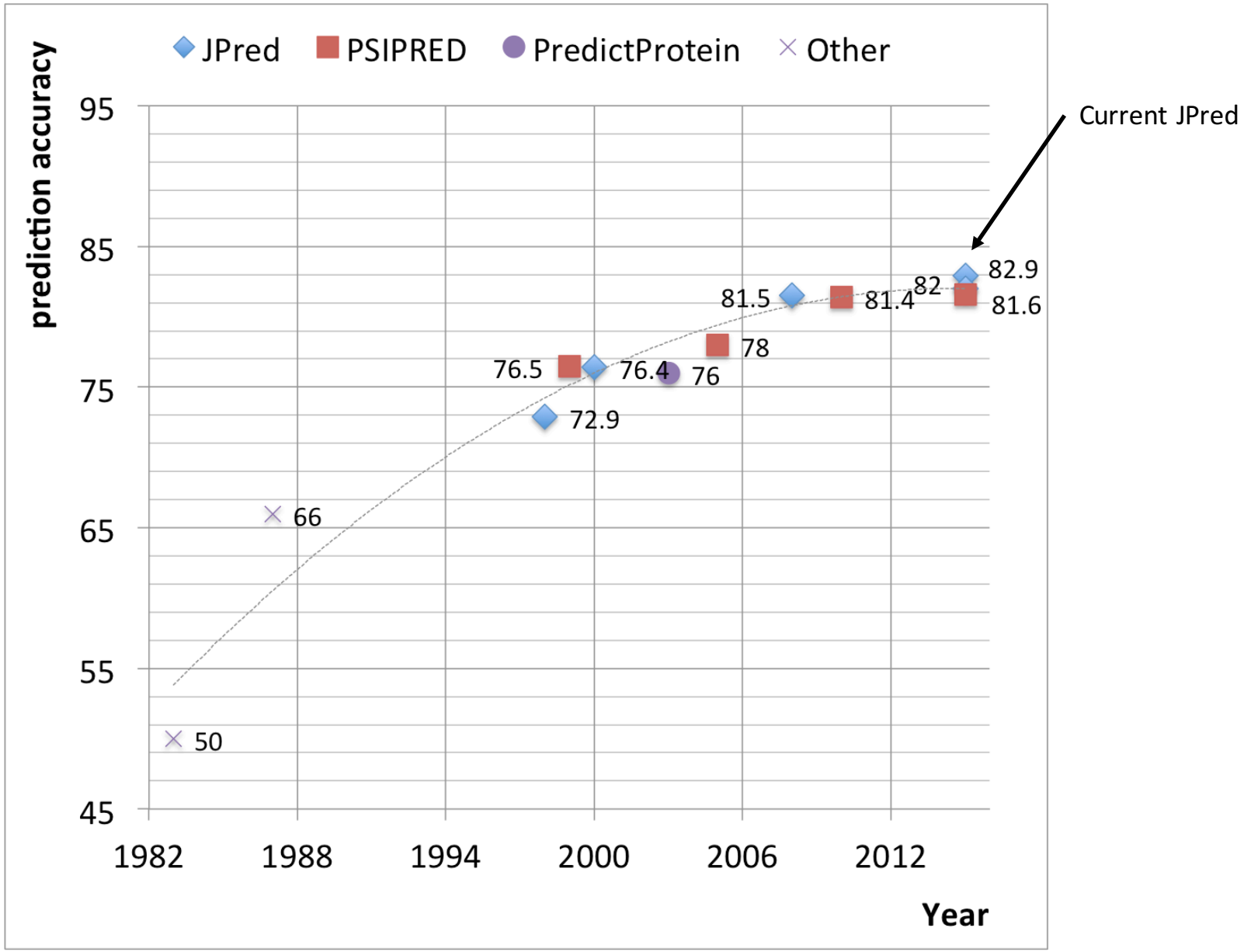
Comparison of JNet Version 1.0 to other Prediction Methods in a Blind Test - (406 proteins)



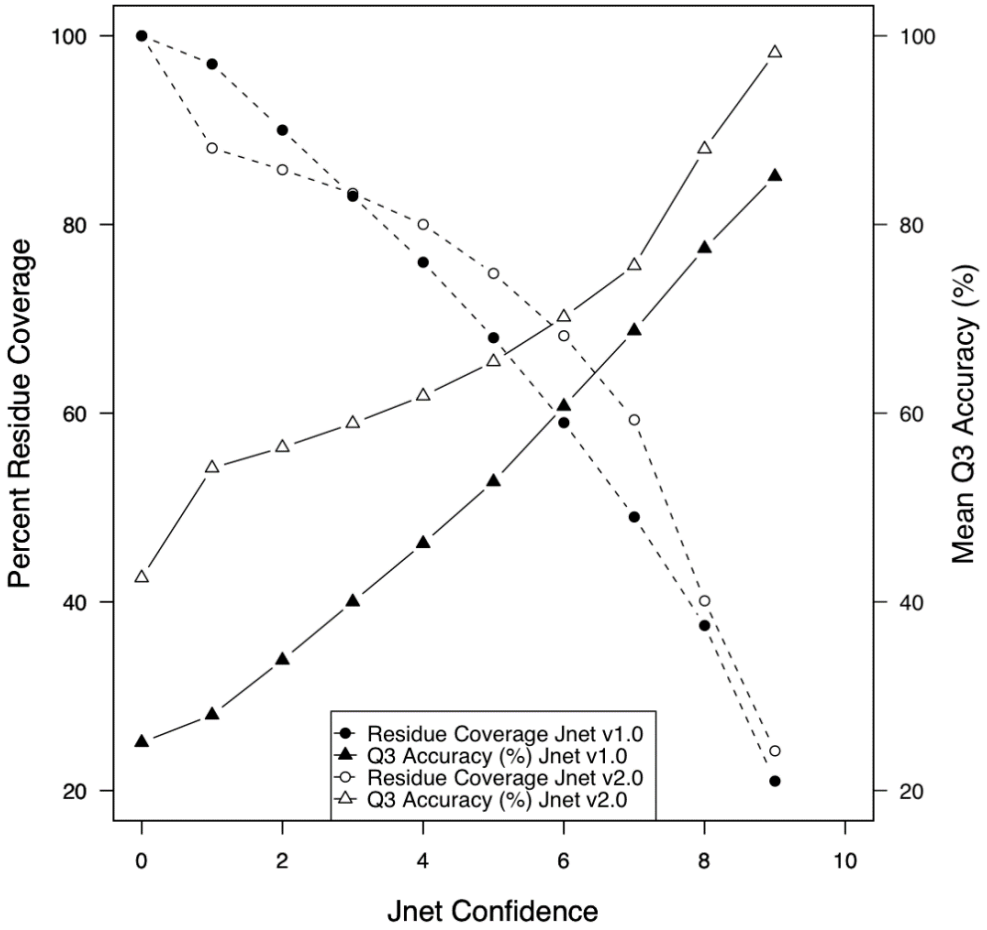
Cuff, J. A. & Barton, G. J., (2000), *Proteins 40: 502-511.*

That was in 2000
What has happened since?

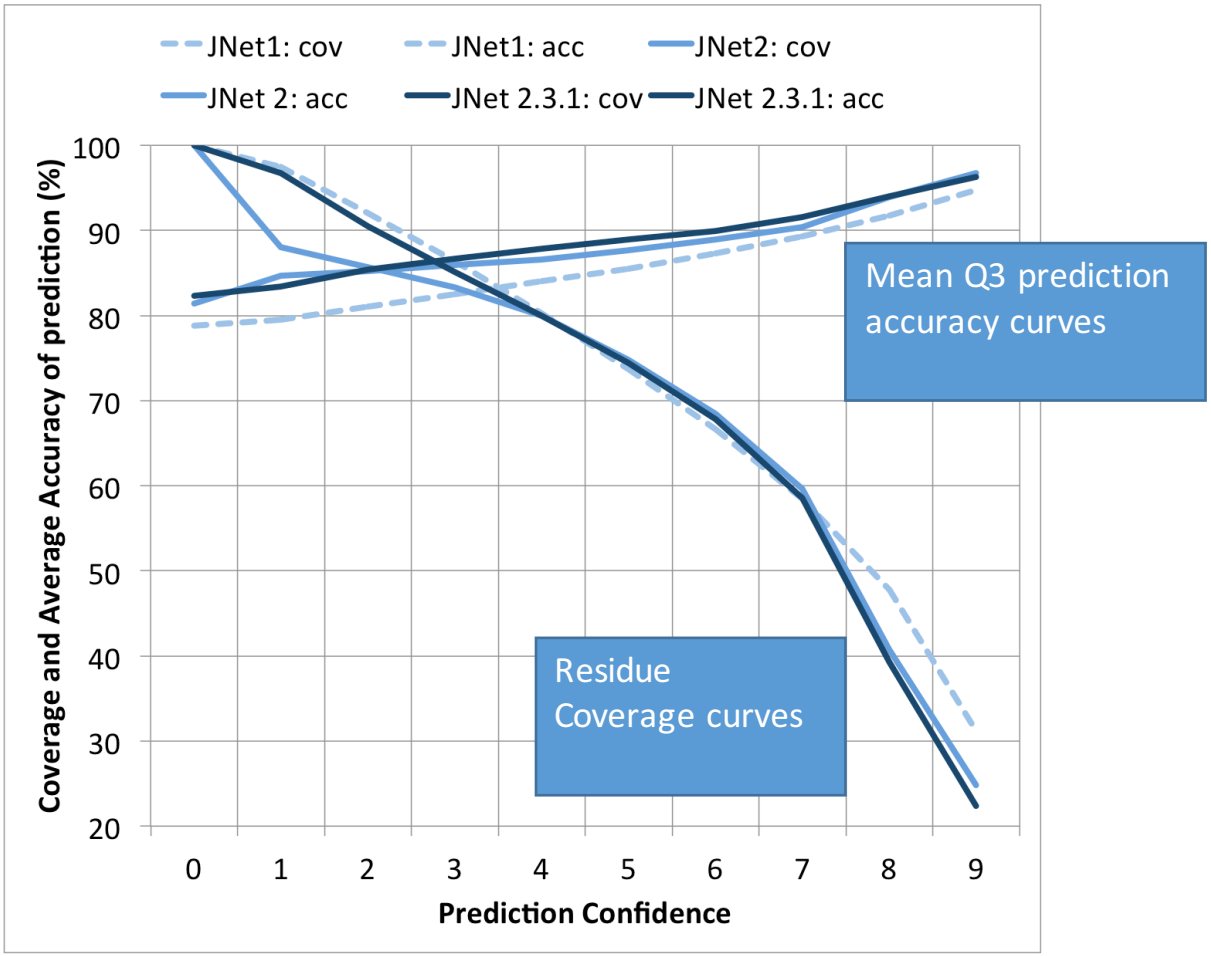
Average Prediction Accuracy is Rising, but Flattening off



Confidence in prediction. JNet 1.0 vs Jnet 2.0



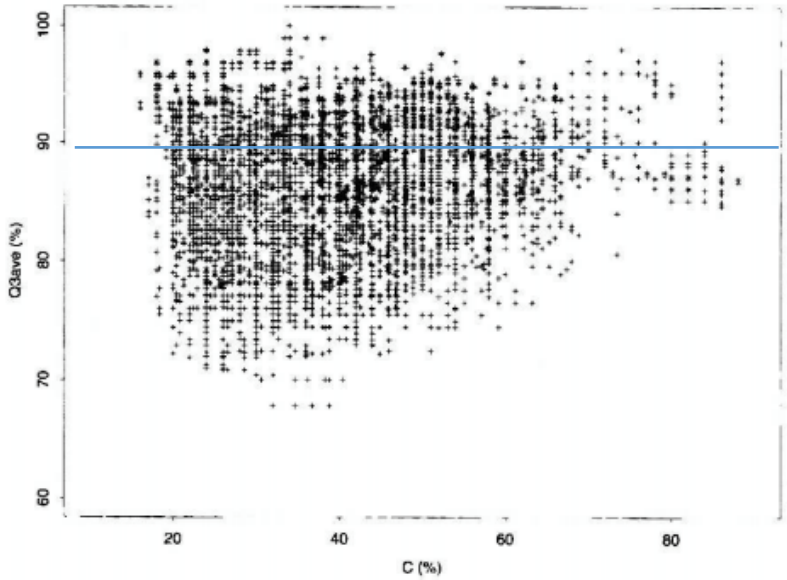
Latest Jnet…


JNet1: cov
JNet1: acc
JNet2: cov
JNet 2: acc
JNet 2.3.1: cov
JNet 2.3.1: acc
Coverage and Average Accuracy of prediction (%)
100
90
80
70
60
50
40
30
20
0
1
2
3
4
5
6
7
8
9
Prediction Confidence
Mean Q3 prediction accuracy curves
Residue Coverage curves

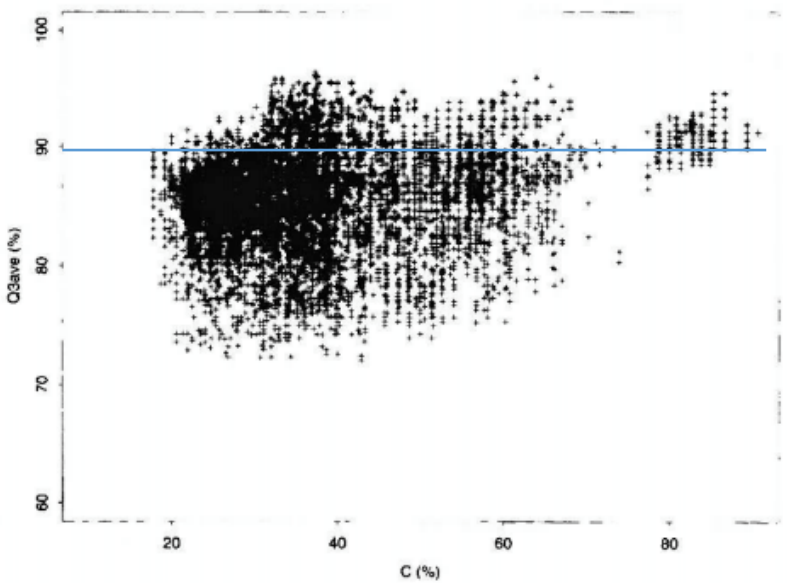
Introducing the Practical

- At last!

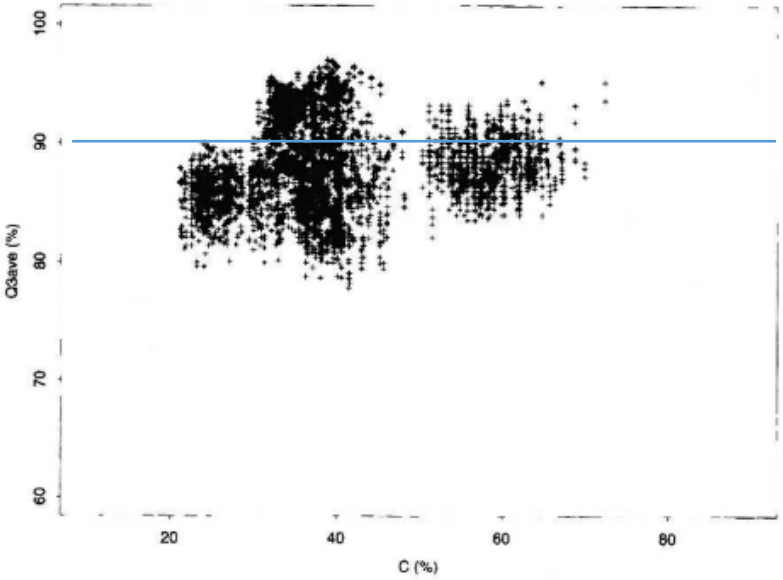
a) length <=50



b) length 51 - 100



c) length 101 - 150



d) length > 150